Original Article

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Efficacy of Different Doses of Dexamethasone as Pre-emptive Analgesia in Patients Undergoing Total Abdominal Hysterectomy under General Anaesthesia: A Prospective Non Randomised Placebo Controlled Study

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ABSTRACT

Introduction: Pre-emptive analgesia reduces postoperative analgesic requirement, avoiding side-effects that occur with parenteral narcotics. Dexamethasone, a long acting synthetic corticosteroid with predominantly glucocorticoid activity is one of the entities used for pre-emptive analgesia. The optimum dose of dexamethasone for pre-emptive analgesia is not defined.

Aim: To study the efficiency of different (low, intermediate and high) doses of dexamethasone as pre-emptive analgesia in patients undergoing total abdominal hysterectomy under general anaesthesia.

Materials and Methods: The prospective non randomised placebo controlled dose range study was conducted in the Department of Anaesthesiology, at a tertiary care institute at Srinagar, Jammu and Kashmir, India, over a period of two years from July 2017 to June 2019. Eighty female patients (age 40-65 years, American Society of Anaesthesiologists (ASA) I and II) scheduled for total abdominal hysterectomy were divided into four groups (Groups A, B, C and D) on the basis of dexamethasone dose. Group A with low dose (0.1 mg/kg), group B with intermediate dose (0.12-2 mg/kg), group C with high dose (>0.2 mg/Kg) and group D with no dexamethasone. Early and late acute postoperative pain {Visual Analog Scale (VAS) score}, cumulative analgesic consumption upto 24 hours, intraoperative blood sugar levels, Postoperative Nausea and Vomiting (PONV), and adverse events were recorded. Analysis of variance (ANOVA) was used for intergroup comparison of means and Chi-square test was used for categorical variables.

Results: The mean age (years) of group A was 52.3±8.87, group B was 48.3±5.23, group C was 49.8±6.85 and group D was 51.7±4.46. Postoperative VAS score for 0 hour, 1 hour, 2 hour, 3 hour, 4 hour was more in patients who had not received dexamethasone pre-emptively (p-value <0.05). VAS score at 6 hour, 12 hour, 24 hour was more in patients who had not received dexamethasone pre-emptively. There was a statistically significant difference in VAS score at 6, 12, 24 hours when low dose dexamethasone group was compared with intermediate and high dose dexamethasone groups (p-value <0.05). Rescue analgesia consumption was significantly less in patients who received intermediate to high dose dexamethasone. Blood sugar levels increased significantly in patients receiving dexamethasone, but returned to baseline after 24 hours. The incidence of nausea and vomiting and the need for rescue antiemetic was significantly less in patients receiving dexamethasone (p-value <0.05). The incidence of postoperative adverse effects was not different among these groups (p-value >0.05).

Conclusion: Intermediate and high dose dexamethasone, given preoperatively in patients undergoing abdominal hyster-ectomy produces better postoperative analgesia with added antiemetic benefit.

Keywords: Hyperglycaemia, Postoperative pain, Visual analogue score

INTRODUCTION

The relief of postoperative pain in surgery represents one of the clinical areas in which precise standardisation does not exist despite the enormous mass of data published in literature. Effective management of postoperative pain helps in early recovery, discharge and less postoperative complications [1,2]. The concept of pre-emptive analgesia is now widely accepted. It helps in reducing the need of analgesic requirement in postoperative period, helps in avoidance of potentially deleterious side-effects that may occur with parenteral administration of narcotics. The term pre-emptive analgesia is defined as analgesia given before a painful stimulus is initiated. Pre-emptive analgesia has its origins in the idea that the painful stimuli, if not prevented by administration of preoperative analgesic drugs, could lead to spinal sensitisation and neuroplasticity processes, resulting in increased pain intensity and duration after surgery [1,3-5].

Dexamethasone is a long acting synthetic corticosteroid with predominantly glucocorticoid activity. Dexamethasone is most commonly used perioperatively to reduce Postoperative Nausea and Vomiting (PONV). Studies have established dexamethasone as a viable option for multimodal analgesia. Mohtadi A et al., observed that a single preoperative dose of 0.1 mg/kg intravenous dexamethasone led to less pain intensity in patients undergoing laparoscopic cholecystectomy [6]. Dexamethasone (8 mg) efficiently reduced postoperative pain severity and the need for analgesic consumption after cesarean section in a study by Shahraki AD et al., [7]. However, different doses of dexamethasone have been used in these studies. The dose to achieve optimal analgesic effects of this medication is not defined. Keeping in view the analgesic property of dexamethasone and lack of proper guidelines for optimum analgesic dose of dexamethasone, this study was conducted to see the efficiency of different doses of dexamethasone as pre-emptive analgesia in patients undergoing total abdominal hysterectomy.

The primary outomes were to see the efficacy of dexamethasone on early acute postoperative pain score {Visual Analog Scale (VAS) score} at 0-4 hours and late acute postoperative pain score (visual analogue scale) at 6, 12, 24 hours postoperatively, and to

see the cumulative analgesic consumption (up to 24 hours) in the postoperative period. The secondary outcomes were to study the incidence of PONV and adverse events during hospital stay including postoperative infection (wound, urinary tract, and pneumonia), hyperglycaemic events, delayed healing and pruritus.

MATERIALS AND METHODS

This prospective non-randomised placebo controlled dose range study was conducted in the Department of Anaesthesiology, at Sher E Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India, over a period of two years from July 2017 to June 2019. Institutional Ethics Committee approval (IEC No-1131/2019-448) and informed written consent was taken from all the patients.

Sample size calculation: Sample size estimation was done using G POWER software (v 3.0.1.0; Franz Faul Keil University, Keil, Germany). It was estimated that the least number of patients required in each group with 80% power, effect size of 0.38 and 5% significance was 20. As there were four groups in this study so 80 patients were included in the study.

Inclusion criteria: Eighty female patients undergoing total abdominal hysterectomy for benign gynaecological conditions with American Society of Anaesthesiologists (ASA) status I and II, between the ages of 40-65 years were included in the study.

Exclusion criteria: Diabetic/hypertensive patients, patients having a history of any cardiac disease, liver disease, renal disease, seizure disorder, patients taking Nonsteroidal Anti-inflammatory Drugs (NSAIDs), opioids or any kind of analgesics or patients already taking steroids were excluded from the study.

Study Procedure

Preanaesthetic visit was performed prior to the day of surgery; patients were prepared by overnight fasting. In the operation theatre, intravenous (i.v.) line was established with 16G or 18G cannula and non dextrose containing solution was infused. All basic standard monitoring was attached {Electrocardiography (ECG), Human Non-invasive Blood Pressure (NIBP), End tidal carbon dioxide ($ETCO_2$), Saturation of Peripheral Oxygen (SpO_2)}. Patient received different dose ranges of dexamethasone before induction. Dose ranges were:

Group A- patients received dexamethasone in low dose (0.1 mg/kg).

Group B- patients received dexamethasone in intermediate dose (0.12-0.2 mg/kg).

Group C- patients received dexamethasone in high dose (>0.2 mg/kg).

Group D- patients received no dexamethasone at any time.

Allocation of patients into different groups was done non randomly at the discretion of the anaesthesiologist.

All doses of dexamethasone were given in 50 mL of normal saline prior to induction of anaesthesia. Preoperative blood sugar was noted in all patients. All patients received preoperative i.v. antibiotic (1 gm of first generation cephalosporin) and pantoprazole 40 mg. All patients had a standardised general anaesthesia procedure. Induction was done using i.v. midazolam (1.5 mg), fentanyl 2 µg/kg body weight, propofol (2 mg /kg body wt) and rocuronium (0.6-1.2 mg/kg). Anaesthesia was maintained with 1 to 2 % isoflurane and 50% oxygen with 50% nitrous oxide. All patients received morphine (0.1 mg/kg) for perioperative analgesia. Neuromuscular blocking was maintained with rocuronium (0.1 mg/kg body weight). All patients were monitored with indirect determinators of arterial pressure and heart rate using standard technique as well as expired CO_2 content and oxygen blood saturation. After procedure, neuromuscular blockade was reversed with neostigmine 60 mcg/kg and glycopyrrolate 10 mcg/kg. Postoperative pain scores and side-effects were recorded by an anaesthesiologist who was not aware of group allocation and dose of dexamethasone received.

Parameters assessed: Effect of dexamethasone on postoperative pain, PONV, intraoperative blood sugar and other side-effects like postoperative infections (wound, urinary tract, pneumonia), hyperglycaemic events, delayed healing, pruritis were noted. Postoperatively early acute pain was assessed using visual analogue scale at 0 hour, 1 hour, 2 hour, 3 hour, 4 hour, and late acute postoperatively pain was assessed using visual analogue scale at 6 hour, 12 hour, 24 hour. Rescue analgesic was given as i.m. ketorolac (30 mg) on demand. The incidence of PONV was recorded immediately on return to the recovery room and at 6, 12 and 24 hours after the operation using a 4 point ordinary scale (0=none, 1=nausea, 2=nausea with request for antiemetic, 3=vomiting). Rescue antiemetic ondansetron (4-8 mg) was given on demand. Blood glucose monitoring was done immediately before induction and after giving i.v. dexamethasone hourly for 4 hours, 4 hourly for 24 hours and every day for the duration of hospital stay.

STATISTICAL ANALYSIS

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, Illinois, USA). Statistical software SPSS (version 20.0) and Microsoft Excel were used to carry out the statistical analysis of data. Continuous variables were expressed as mean±SD and categorical variables were summarised as percentages. Analysis of Variance (ANOVA) was employed for inter group analysis of data and for multiple comparisons, Least Significant Difference (LSD) test was applied. Chi-square test or Fisher's-exact test, whichever appropriate, was used for comparison of categorical variables. A p-value <0.05 was considered statistically significant. All p-values were two tailed.

RESULTS

All the groups were homogenous with reference to age, weight, height, Body Mass Index (BMI), duration of surgery. There was no statistically significant difference with respect to ASA grading and duration of surgery among these groups (p-value >0.05) [Table/Fig-1]. The pain score VAS assessed postoperatively for early acute postoperative pain at 0 hour, 1 hour, 2 hour, 3 hour, 4 hour was more in patients who had not received dexamethasone pre-emptively. The VAS score was statistically significant when compared among these groups at all times (p-value <0.05).

Parameters	Group A (Mean±SD)	Group B (Mean±SD)	Group C (Mean±SD)	Group D (Mean±SD)	p-value
Age (years)	52.3±8.87	48.3±5.23	49.8±6.85	51.7±4.46	0.202*
Weight (kg)	61.6±7	58.3±8.67	62.7±8.92	57.6±5.93	0.118*
Height (cm)	154.3±4.29	152.4±4.99	155.1±4.55	151.9±3.63	0.053*
Body mass index (kg/m^2)	25.92±3.47	25.16±4.12	26.08±3.72	24.98±2.79	0.706*
ASA status (I/II) (%)	40/60	40/60	45/55	30/70	0.801**
Duration of surgery (min)	121.9±27.42	112.3±23.65	108.8±8.77	110.3±13.81	0.223*

[Table/Fig-1]: Showing comparison of demographic parameters, ASA status and duration of surgery among the groups.
*p-value calculated using ANOVA; **p-value calculated using Chi-square test

The pain score for acute postoperative pain was highest in patients who had not received dexamethasone (Group D) and lowest for patients receiving high dose (Group C) and intermediate dose (Group B) dexamethasone. Pain score for late postoperative pain were highest in patients not receiving dexamethasone (Group D) and lowest in patients who received high dose dexamethasone (Group C) and intermediate dose dexamethasone (Group B). Pain scores were comparable between intermediate (Group B) and high dose (Group C) dexamethasone groups [Table/Fig-2]. The cumulative rescue analgesic (intramuscular ketorolac) requirement was significantly less in intermediate (Group B) and high dose range (Group C) dexamethasone group as compared to groups who had

Parameters	Time interval	Group A (Mean±SD)	Group B (Mean±SD)	Group C (Mean±SD)	Group D (Mean±SD)	p-value
Early acute postoperative pain	0 hour	0.45±0.510	0.35±0.489	0.20±0.410	1.95±0.686	0.001*
	1 hour	1.65±0.745	0.80±0.616	0.45±0.759	2.25±0.786	0.001*
	2 hour	2.30±0.657	1.45±0.510	0.80±0.768	3.25±1.020	0.001*
	3 hour	3.10±0.641	2.20±0.696	1.55±0.686	3.70±1.031	0.001*
	4 hour	3.25±0.550	2.85±0.637	2.25±0.786	3.70±0.801	0.001*
Late acute postoperative pain	6 hour	4.40±0.754	3.05±1.052	2.85±0.745	4.65±0.671	0.001*
	12 hour	4.55±0.826	3.35±0.671	3.15±0.745	4.75±0.851	0.001*
	24 hour	4.65±0.061	3.85±0.745	3.55±0.945	4.80±0.768	0.001*
Rescue analgesia consumption (mg)		81±25.94	39±17.14	36±12.31	92±15.31	0.001*

[Table/Fig-2]: Showing comparison of early and late acute postoperative pain, rescue analgesia consumption among the groups.
*Statistically significant, p-value calculated using ANOVA

received low dose dexamethasone (Group A) or no dexamethasone at all (Group D) (p-value <0.05).

There was a significant increase in blood sugar levels in patients who had received dexamethasone at any dose range. Mean blood sugar increase in low (Group A), intermediate (Group B), high dose (Group C) and no dexamethasone group (Group D) was 35.30 mg/dL, 81.60 mg/dL, 89.20 mg/dL and 23.1 mg/dL, respectively. In low dose dexamethasone group, blood sugar level peaked at 8 hours and started declining after 8 hours and returned to baseline by 24 hours. In high and intermediate dexamethasone groups, blood sugar level peaked at 8 hours and started declining after 12 hours and returned to baseline by 24 hours [Table/Fig-3].

Time interval	Group A (Mean±SD)	Group B (Mean±SD)	Group C (Mean±SD)	Group D (Mean±SD)	p-value
Baseline	97.1±11.61	97.9±15.78	94.1±13.09	95.3±7.84	0.771
0 hour	102.8±9.27	109.6±15.73	112.1±10.38	101.4±7.54	0.007*
1 hour	108.2±7.71	112.6±15.73	115.4±12.50	103.7±10.35	0.016*
2 hour	112.6±6.75	127.5±13.95	130.4±10.54	110.5±9.41	0.001*
3 hour	117.2±7.71	140.1±13.56	143.1±9.02	114.7±9.86	0.001*
4 hour	124.6±6.75	157.2±14.03	161.4±10.54	118.4±9.58	0.001*
8 hour	132.4±6.49	179.2±15.82	183.3±15.38	103.1±7.04	0.001*
12 hour	104.8±9.27	137.3±13.49	141.1±9.02	101.4±9.58	0.001*
16 hour	101.4±8.35	102.9±15.78	104.3±10.11	100.1±7.63	0.658
20 hour	98.1±9.32	101.1±15.93	102.2±9.83	99.4±8.25	0.677
24 hour	97.4±8.89	97.1±14.82	98.1±10.17	96.1±7.32	0.950

[Table/Fig-3]: Showing comparison of blood sugar levels at various intervals among the groups.
*Statistically significant, p-value calculated using ANOVA

The incidence of nausea and vomiting was more in patients who had not received dexamethasone. It was observed that rescue antiemetic was needed in 70% of patients who had not received dexamethasone (Group D) at any time and there was minimum antiemetic requirement (5 %) who had received dexamethasone at high dose (Group C) [Table/Fig-4]. The incidence of postoperative adverse effects were statistically insignificant when compared among these groups (p-value >0.05) [Table/Fig-5].

Parameter	Group A	Group B	Group C	Group D	p-value
Nausea	5 (25%)	3 (15%)	2 (10%)	12 (60%)	0.006
Vomiting	2 (10%)	1 (5%)	1 (5%)	8 (40%)	0.004
Rescue antiemetic requirement	4 (20%)	3 (15%)	1 (5%)	14 (70%)	0.001*

[Table/Fig-4]: Showing comparison of postoperative nausea, vomiting and rescue antiemetic consumption among the groups.
*p-value calculated by Chi-square test

Side-effects	Group A	Group B	Group C	Group D	p-value
Wound infections	0	2 (10%)	1 (5%)	1 (5%)	0.551
UTI	0	0	0	0	-
Pneumonia	0	0	0	0	-
Hyperglycaemic events	0	0	0	0	-
Delayed healing	0	1 (5%)	0	1 (5%)	0.562
Pruritis	0	0	0	0	-

[Table/Fig-5]: Showing postoperative side-effects among the groups.
p-value calculated by Chi-Square test

DISCUSSION

Acute postoperative pain can delay functional recovery for patients undergoing surgical procedures. Pre-emptive analgesia has been used as an important strategy to mitigate postoperative pain. The objective of the present study was to assess the efficacy of pre-emptive use of dexamethasone in different dose ranges (low, intermediate and high dose) on postsurgical pain outcomes in patients undergoing total abdominal hysterectomy under general anaesthesia.

The main finding of this study was that pre-emptive use of intravenous dexamethasone reduces acute early and late postoperative pain in all the dose ranges. A better pain relief was observed with intermediate dose (0.12-2 mg/kg) and high dose (>2 mg/kg) dexamethasone, both in terms of VAS score and rescue analgesia consumption.

Systemic administration of dexamethasone has an analgesic action and is due to inhibition of production of inflammatory mediators. It acts by inhibiting cyclooxygenase enzyme activity and also inhibits the same chain reactions that degrade phospholipids released by surgically injured cell membranes, leading to the production of important pro-inflammatory mediators [8]. Dexamethasone reduces the levels of prostaglandin E2, and is effective in controlling inflammation and postoperative pain [9]. Pain and inflammation are consequences of the release of chemical mediators produced after tissue trauma, therefore it would be reasonable to conclude that pre-emptive medication contributes to lowering the concentration of these mediators in tissue, and the presence of the drug in the blood stream inhibits their initial production. As a result, the lower the tissue concentration of these mediators the lower will be inflammatory response [10,11]. This may explain the significantly less pain score (VAS score) in patients who had received intravenous dexamethasone in intermediate and high dose range.

The analgesic effect of pre-emptive dexamethasone has been described in several studies. However, the optimal dosage of dexamethasone for analgesia is still a subject of debate. Mohtadi A et al., observed that single dose 0.1 mg/kg (up to 8 mg) of intravenous dexamethasone, led to less pain intensity and amounts of meperidine consumption, in comparison with placebo [6]. A systemic review by Waldron NH et al., involving 5796 patients who had received dexamethasone 1.25-20 mg concluded that perioperative single-dose dexamethasone was associated with statistically significant reductions in postoperative pain, postoperative opioid consumption, need for rescue analgesia, PACU stays, and a

longer time to first analgesic dose. They also analysed dose effect relationship by deriving a mg/kg dose and dividing the studies into low (<0.1mg/kg), intermediate (0.11-0.20 mg/kg), high (>0.21mg/kg) dose dexamethasone, then performed pair wise subgroup analysis and found that intermediate and high dose but not low dose dexamethasone reduced 24 hour opioid consumption compared with placebo [12].

Another finding of this study was that patients who had received dexamethasone at any dose range had lesser incidence of PONV. This observation correlates with Rodrı´guez PE et al., who observed that the preoperative dexamethasone (8 mg) ameliorated nausea, vomiting, pain, and fatigue after elective laparoscopic cholecystectomy without apparent side-effects [13]. Koh JI et al., observed that the concomitant use of dexamethasone (10 mg) reduced postoperative pain and PONV after total knee arthroplasty [14]. Sekhavat L et al., also observed that prophylactic administration of 8mg of dexamethasone reduced the postoperative frequency of PONV in women undergoing abdominal total hysterectomy [15]. Hermans V et al., observed that dexamethasone (0.15 and 0.5 mg/kg) at the induction of anaesthesia was effective in reducing the incidence of early and late PONV in paediatric patients undergoing tonsillectomy [16]. They also commented that the minimum dose of dexamethasone that reduces vomiting still remains undetermined. A dose finding study observed 2.5 mg to be minimum effective dose for preventing postoperative vomiting in patients undergoing gynaecological surgery [17] whereas subsequent studies found 5 mg to be the minimum effective dose in patients undergoing thyroidectomy [18]. In the present study, all dose ranges of dexamethasone were equally efficacious in reducing the incidence of nausea and vomiting. A high dose dexamethasone did not offer any advantage over intermediate and low dose dexamethasone for relief of PONV. Furthermore, intermediate and high dose dexamethasone were equally efficacious in reducing postoperative pain. So, intermediate dose dexamethasone appears to be better for optimal analgesia and antiemesis.

Although a significant increase in blood glucose levels was seen after intermediate and high doses of dexamethasone (70-80 mg/dL from baseline) and low dose dexamethasone (30-35 mg/dL), the blood glucose levels returned to normal after 24 hours. Also there was no significant difference in incidence of wound infection and delayed wound healing among the groups. The administration of dexamethasone 4 mg i.v. facilitated recovery to “home readiness” in outpatients undergoing anorectal surgery because a single dose of dexamethasone failed to increase wound complications in this high-risk patient population in a study by Coloma M et al., [19]. Waldron NH et al., in their meta-analysis observed that perioperative single-dose dexamethasone was not accompanied by an increased risk of infection or delayed wound healing [12]. Dexamethasone induces hepatic gluconeogenesis and insulin resistance, thereby causing transient hyperglycaemia, which can lead to oxidative stress and endothelial and innate immune dysfunction [20,21]. Acute, short-term hyperglycaemia affects all major components of innate immunity and impairs the ability of the host to combat infection resulting in increased risk of wound infection and delayed wound healing in patients [21]. The anti-inflammatory and immunosuppressive properties of corticosteriods (e.g., inhibition of pro-inflammatory cytokines, reduced ability of leucocytes to enter sites of infection, tissue injury, inhibitory effects on T and B cells) also have a negative effect on wound healing and might increase the risk of infection with long-term treatment [22]. Although increased blood sugar levels were observed with all single preoperative dose ranges of dexamethasone, this did not lead to delayed wound healing or increased wound infections as seen with long term corticosteroid use. Thus, a single pre-operative dose of dexamethasone can be used safely without increasing the risk of these complications.

Limitation(s)

Randomisation was not done in this study, which could lead to selection bias. To reduce bias, the anaesthesiologist recording postoperative pain scores and other parameters was blinded to group allocation. Also, the study duration was limited to 24 hours postoperatively, so effect of dexamethasone on chronic pain could not be studied.

CONCLUSION(S)

It can be concluded that intermediate and high dose range of dexamethasone but not the low dose range, given preoperatively in patients undergoing abdominal hysterectomy produces better analgesia in the postoperative period. Dexamethasone has an added advantage as an antiemetic. The authors recommend intermediate dose range (0.12-0.2 mg/kg) of dexamethasone as pre-emptive analgesic.

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